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Immunosenescence and Aging

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ABSTRACT

Changes occur in both the adaptive and innate immune functions as human aged. This is termed immunosenescence. It is defined as age-associated changes in the immune response. There is a general misconception about the immune system of the elderly that becomes hypo- responsive or non-functional. However, although there are many different idea about immunity decline, this does not occur completely but some activity of the aging immune response are preserved. The relationships between aging and the immunity are manifest at multiple levels that include reduced T and B cells. As a result, elderly people do not respond to immune challenge as strong as the young. A major aim of aging studies is to determine the molecular and cellular changes during activity of the immune system. This information has been used for clinical trials to preserve the aging immune system.

Keywords: immunosenescence, Inflammaging, Aging, Immunity, Thymus, Cytokines

INTRODUCTION

Increasingly, strong evidence demonstrates that aging is accompanied by severe changes in the immune system. Some changes occur in ageing immune system that is also known as immunosenescence. Commonly, there is a misconception that the immune system of the elderly

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becomes hypofunctional. Although there are many reasons of immunity decline, this does not occur uniformly. Some suggested that "senescent immune remodeling" should be used instead of the term "immunosenescence" to be well understood of the aging immune system. The changes in the immune system in aging are antibody production, cell replicative capacity, alterations in T-lenfosit subpopulation size and cytokine secretion, the number of T cells, the CD4 + / CD8 + ratio with the involution of the thymus, antibody-responsive B-cells and antigen presented by dendritic cells. In addition to these changes, natural killer cells that eliminate infected cells, and monocytes and macrophages and T cell repertoire decrease the diversity of the cells. As a result of these changes, it is a proinflammatory state called "inflammaging" with a decrease in response capacity to new antigens [1-4].

Even though there is a difference between individuals with aging, they have more than three chronic diseases in 25% of individuals aged 65 years and older and at least one disease in 80% of them. While some are in a more comfortable aging, some of them need to undergo strict treatment and care. These differences are associated with many reasons such as malnutrition, inadequate physical activity, loss of mechanical barrier function, as well as the contribution of processes such as inflammation, dysregulation of a variety of homeostatic mechanisms and oxidative stress [5-7].

NAD (Nicotinamide Adenine Dinucleotide) dependent deacetylation enzymatic reactions can be adversely affected by "Sirtuins" or "SIRT (1-6)", which protects against oxidative stress with aging and reduces cellular dysfunction and protects against age-related pathologies. It has been suggested that SIRT (1-6) proteins have been shown to have a positive effect on mitochondrial functions and DNA repair [8-12].

AGE-ASSOCIATED CHANGES IN IMMUNE FUNCTIONS

Throughout lifespan, inflammatory mediators play an important role in responding to pathogens or infections. However, this response is negatively affected by aging, and studies on inflammation / oxidative stress get increased senescence, mitochondrial dysfunction and reduced stress resistance are increasing [3]. In some cases like cytomegalovirus (CMV) infection, virus remains in a persistent state. This causes permanent differentiation of CD8 + cells and inflammation [13]. And also, tumor necrosis factor (TNF) and various pro-inflammatory interleukins were found to be higher in the elderly [14]. In fact there are many opinions for the pro-inflammatory situation. Increased lifespan of tissue cells during chronic viral infections such as cytomegalovirus, and increasing lifespan of macrophage in the elderly is defined as chronic inflammation called inflammaging. However, viral infections such as CMV may negatively affect the oligoclonal memory cells and deplete the naive T cell pool. Therefore, immunity is abnormal in the elderly and causes an adaptive response to pathogens to be less effective [15-17].

After the bone marrow and thymus are produced, naive B and T cells migrate to secondary lymphoid tissues such as spleen. While the formation of various immune repertoires occurs

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strongly in young people, because of thymus involution the immune repertoire and relative decrease in memory B cells population in elderly [18-20]. In addition, malfunctioning leukocyte and erythrocyte precursors lead to anaemia predisposition [21, 22]. In fact, there are many reasons for this decline in relation to age. These include hematopoietic stem cells (HSCs), progenitor cells, local tissue and systemic environments [23-26]. HSCs are affected by age-related impaired adherence to stromal cells and stem cell cells [27]. HSCs demonstrate that lymphoid progenitor is lost and long-lived myeloid progenitor accumulates in aged. However, myeloid progenitor HSCs from young to aged sources behave similarly in all studies [28]. The reason for the decrease in the number of lymphoid progenito HSCs by aging is not clear. Structurally programmed events in stem and progenitor cells may be related to having some sort of internal clock that regulates the functions and life of these cells. Although the results suggested that the decrease in lymphopoiesis is affected by age-related environmental changes, it is not precisely determined [29]. In addition, it has been suggested that epigenetic changes such as DNA damage, telomere shortening, age-related inflammation may play a role [30, 31]. In some studies, it has been proposed some changes such as important functional and numerical changes, including surface receptor expression and antigen presenting cells, while others suggest that changes are occurred with migration to local lymph nodes [32, 33]. Whether or not T cell proliferation changes with aging in vitro models is confounding, but in vivo models, antigen presentation and decrease in T cell proliferation have been demonstrated [32, 34]. With the increase of prostaglandin D2 with aging, reduction of cytokine receptor presentation required is observed to activate dendritic cells in the lungs and migrate to the lymph nodes [34].

AGING AND THYMUS

Age-related changes in thymus are associated dendritic cells, fibroblasts, macrophages and thymic epithelial cells, and thymic epithelial cells decrease in by and by [35]. In addition, it is suggested that inflammatory mediators and also thymocytotoxics may increase with aging [36]. There are also systemic changes in lymphocyte production and there is a decrease in the synthesis of growth hormone and IGF-1 hormones, which stimulate thymopoiesis, by aging. Consequently, there are age-related changes in the endocrine system and a decrease in lymphopoiesis [26, 37-39]. T lymphocyte education in thymus is disrupted by thymic involution, which continues from birth to the age of 50 years. As a result, naive T cells are greatly reduced. Thus, these cells are inadequate to respond to new antigens with a limited number of receptors. As a result of thymic involution, T cells return predominantly to the dominance of CD8 + T cell population phenotype with less clonal expansion ability than naive T cells. However, the functionality of lack of naive CD8+ T cell numbers in the elderly do not correlate with ageing during acute and chronic viral infections. Although the antigenic diversity of CD4 + T cells decreases more rapidly than CD + 8, age-related changes can be affected by the genetic background and environmental exposure [40].

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INFLAMMAGING

Inflammaging is defined as a progressive increase in proinflammatory status. IL-6 and TNF-α accumulates in the tissues during aging. These mediators are suggested to be associated with cells called senescence-associated secretory phenotype (SASP) [41]. Besides a new concept of "anti-inflammaging" was also proposed that influences progressive pathophysiological changes, as well as lifespan, and acts along with inflammaging [42]. When there is the inflammation, a series of complex responses occur to both pathogens and tissue injury and the inflammatory response disappears resolving inflammation with the elimination of proinflammatory factors. Because of cells getting old or DNA damage, SASP cells are formed and inflammatory mediators increase such as IL-6. However, the source of inflammatory mediators may be different from one to another. Microenvironmental factors such as dendritic or stromal cells in relation to age are a shift from a salutary to an inflammatory environment [43, 44]. Depending on age, naive CD + 4 cells differ to Th17 instead of Th1 and Th2. Inflammatory mediators are stimulated by Th1 and Th2 and affect stromal cells and other environmental population [45]. In fact, the immune response like inflammation is a physiological response of the body. Normally, inflammatory and anti-inflammatory cytokines are in a dynamic equilibrium and maintain inflammation at a physiological border. A moderate inflammatory response is beneficial for the body but an excessive response is harmful. Inflammation, which is a determinant of aging speed and lifespan, decreases the quality of life and increases morbidity and mortality. In fact, it is useful for the neutralization of cytokines in the early stages of life, but in the later stages it is harmful.

In fact, it is useful for the neutralization of cytokines in the early stages of life, but in the later stages it is harmful. Some investigators describe decreasing adaptive immunity during aging as immunosenescence that is accompanied by an increase in proinflammation described as inflammaging [46]. Some theories have been suggested for the mechanisms of inflammaging. These are stress, oxidation-Inflammation, cytokines, DNA damage, autophagy and stem cell aging. Inflammation, immune response and stress create a defensive network and innate immunity and stress have a relationship. Stress creates a strong immune response in young people, while a weak response in the elderly. When an excessive stress response occurs, the proinflammatory response increases and causes inflammaging. However, the presence of proinflammatory character as a paradoxal in healthy elderly people has been suggested to indicate a physiological inflammation [47].

According to the Oxidation-Inflammation theory, oxidative stress affects homeostasis, aging and lifespan. The presence of sufficient antioxidants in nutrients reduces oxidative sress and improves immune function and prolongs life [48, 49]. It has been suggested that proinflammatory cytokines such as CD4 + T lymphocytes, CD8 +, IFN-γ, TNF-α and IL-4 participate into the process of inflammation and have an important role in it, this idea called the theory of cytokines [50, 51]. Elevated levels of serum IL-6 and TNF-al are predictive markers in the elderly for inflammation

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and are associated with morbidity and mortality [52]. In a previous study conducted in Italian elderly people, it was detected that in the promoter region of IL-6 gene frequency of the -174C single nucleotide polymorphism (SNP) and in women's IL-10 gene coding frequency of the -1082G SNP increased. These findings indicate that gene polymorphisms of cytokines such as IL-6 and IL-10 play a role in the immune-inflammatory response [53]. Although excessive proinflammatory cytokines may cause immune-inflammatory diseases, moderate levels of proinflammatory cytokines contribute to inducing a protective response. Another theory is associated with DNA damage. With the effect of various factors, it contributes to cellular senesence by causing mutations and chromosomal rearrangements by generating errors in the replication or translation of DNA by telomere and mitochondrial DNA damage. The DNA damage response caused by telomere shortening is a fundamental mechanism involved in the aging process [54]. There is a close relationship between cell senescence and organism aging and there is an increase in proinflammatory secretory phenotype when DNA damage response occurs and the neighbouring cells are affected and inflammation becomes systemic. Increased number of cells with DNA damage response exacerbates inflammation [55, 56].

DNA damage cause and induce inflammaging because stem cells and stromal fibroblasts transform excessive proinflammatory cytokine-presenting cells. Another theory for inflammaging is the "Autophagy". Normally, many pathophysiological harmful and abnormal substances are removed from the cell by transferring them to the cell lysosome. Therefore, homeostasis and normal metabolism are maintained. Mitochondrial disorders occur due to decreasing autophagic cleansing capacity during aging and protein accumulation begins. This increases reactive oxygen species to cause oxidative stress. As a result, IL-1β and IL-18 increase and this contribute to the inflammation and aging [57-60]. Another theory, Stem Cell Aging, is responsible for triggering chronic inflammation. Inflammatory factors activate the JAK / STAT signaling pathways and this causes cells secrete cytokines such as TNFα and IL-1β. This leads to a low level of chronic inflammation and regenerative capacity of stem cells decreases. Inflammation is highly associated with some of the following diseases: Type II diabetes mellitus, osteoporosis, insulin resistance, Alzheimer's disease, atherosclerosis, heart disease, age-related macular degeneration, parkinson's disease, acute lateral sclerosis, multiple sclerosis, and cancer [61-64]. Inflammaging also destruct the colon and gastric mucosa epithelium and causing damage to the regeneration in the cellular and molecular levels [65].

In conclusion, Inflammaging and immunosenescence coexist and it is difficult to distinguish whether inflammation-related diseases are caused by inflammation or immunosenescence so molecular and biological studies are needed.

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References

1. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. J Clin Invest. 2013; 123: 958-965.
2. Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstein B. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis. 2008; 46: 1078-1084.
3. Weinberger B, Grubeck-Loebenstein B. Vaccines for the elderly. Clin Microbiol Infect 2012 Suppl; 18:100-108.
4. Adriana L de Araújo; Léia CR Silva; Juliana Ruiz Fernandes; Gil Benard DISCLOSURES Immunotherapy. 2013; 5: 879-893.
5. Ward BW, Schiller JS. Prevalence of multiple chronic conditions among US adults: estimates from the National Health Interview Survey, 2010. Prev Chronic Dis. 2013; 10: E65.
6. Han L, Allore H, Murphy T, Gill T, Peduzzi P, et al. Dynamics of functional aging based on latent-class trajectories of activities of daily living. Ann Epidemiol. 2013; 23: 87-92.
7. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. J Physiolol. 2015.
8. Tasselli L, Wei Z, Katrin FC. “SIRT6: novel mechanisms and links to aging and disease.” Trends in Endocrinology & Metabolism. 2017; 28: 168-185.
9. Sharma A, Diecke S, Zhang WY, Lan F, He C, et al. The role of SIRT6 protein in aging and reprogramming of human induced pluripotent stem cells. J Biol Chem. 2013; 288:18439-18447.
10. Dominy JE Jr, Lee Y, Jedrychowski MP, Chim H, Jurczak MJ, et al. The deacetylase Sirt6 activates the acetyltransferase GCN5 and suppresses hepatic gluconeogenesis. Molecular cell. 2012; 48: 900-913.
11. Xu Z, Zhang L, Zhang W, Meng D, Zhang H, et al. SIRT6 rescues the age related decline in base excision repair in a PARP1-dependent manner. Cell cycle. 2015; 14: 269-276.
12. Ozkan O, Tural K. “Changes in the Expression and the Role of Sirtuin 3 in Cancer Cells and in Cardiovascular Health and Disease.” Gene Expression and Regulation in Mammalian Cells-Transcription Toward the Establishment of Novel Therapeutics. IntechOpen. 2018.
13. Pawelec G. Immunosenenescence: role of cytomegalovirus. Exp Gerontol 2014; 54: 1-5.
14. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech. Ageing Dev. 2007; 128: 92-105.
15. McElhaney JE, Zhou X, Talbot HK, Soethout E, Bleackley RC, et al. The unmet need in the elderly: how immunosenescence, CMV infection, co-morbidities and frailty are a challenge for the development of more effective influenza vaccines. Vaccine. 2012; 30: 2060-2067.
16. Harper JM, Wilkinson JE, Miller RA. Macrophage migration inhibitory factorknockout mice are long lived and respond to caloric restriction. FASEB J. 2010; 24: 2436-2442.
17. Olivieri F, Rippo MR, Prattichizzo F, Babini L, Graciotti L, et al. Toll like receptor signaling in “inflammaging”: microRNA as new players. Immun. Ageing. 2013; 10: 11.
18. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. Nat Immunol. 2004; 5:133-139.
19. Lynch H, Goldberg G, Chidgey A, Van den Brink M, Boyd R, Sempowski G. Thymic involution and immune reconstitution. Trends Immunol. 2009; 30: 366-373.
20. Steinmann GG. Changes in the human thymus during aging. Curr Top Pathol.1986; 75: 43-48.
21. Dewan SK, Zheng SB, Xia SJ, Bill, K. Senescent remodeling of the immune system and its contribution to the predisposition of the elderly to infections. Chin. Med. J. 2012; 125: 3325-3331.
22. Van Zant G, Liang Y. Concise review: hematopoietic stem cell aging, life span, and transplantation. Stem Cells Transl. Med. 2012; 1: 651-657.
23. Rossi DJ, Bryder D, Zahn JM, Ahlenius H, Sonu R, et al. Cell intrinsic alterations underlie hematopoietic stem cell aging. Proc Natl Acad Sci U S A. 2005; 102: 9194-9199.
24. Zediak VP, Maillard I, Bhandoola A. Multiple prethymic defects underlie age-related loss of T progenitor competence. Blood. 2007; 110:1161-1167.
25. Taub D, Murphy W, Longo D. Rejuvenation of the aging thymus: growth hormone-mediated pathways and ghrelin-mediated signaling pathways. Curr Opin Pharmacol. 2010; 10:408-424.

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26. Song Z, Wang J, Guachalla LM, Terszowski G, Rodewald HR, et al. Alterations of the systemic environment are the primary cause of impaired B and T lymphopoiesis in telomere-dysfunctional mice. Blood. 2010; 115: 1481-1489.

27. de Haan G, Van Zant G. Dynamic changes in mouse hematopoietic stem cell numbers during aging. Blood. 1999; 93: 3294-3301.

28. Cho RH, Sieburg HB, Muller-Sieburg CE. A new mechanism for the aging of hematopoietic stem cells: aging changes the clonal composition of the stem cell compartment but not individual stem cells. Blood. 2008; 111: 5553-5561.

29. Challen G, Boles N, Chambers S, Goodel M. Distinct hematopoietic stem cells subtypes are differentially regulated by TGF-β1. Cell Stem Cell. 2010; 6: 265-278.

30. Tollervey JR, Lunyak VV. Epigenetics: judge, jury and executioner of stem cell fate. Epigenetics 2012; 7: 823-840.

31. Tumpel S, Rudolph KL. The role of telomere shortening in somatic stem cells and tissue aging: lessons from telomerase model systems. Ann. N. Y. Acad. Sci. 2012; 1266: 28-39.

32. Pereira LF, De Souza AP, Borges TJ, Bonorino C. Impaired in vivo CD4+ T cell expansion and differentiation in aged mice is not solely due to T cell defects: decreased stimulation by aged dendritic cells. Mech. Ageing Dev. 2011; 132: 187-194.

33. Grolleau-Julius A, Harning EK, Abernathy LM, Yung RL. Impaired dendritic cell function in aging leads to defective antitumor immunity. Cancer Res. 2008; 68: 6341-6349.

34. Zhao J, Legge K, Perlman S. Age-related increases in PGD (2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. J. Clin. Invest. 2011; 121: 4921-4930.

35. Manley N, Richie E, Blackburn C, Condie B, Sage J. Structure and function of the thymic microenvironment. Front Biosci. 2011; 17: 2461-2477.

36. Chinn IK, Blackburn CC, Manley NR, Sempowski GD. Changes in primary lymhoid organs with aging. Semin Immunol. 2012; 24: 309-320.

37. Taub D, Murphy W, Longo D. Rejuvenation of the aging thymus: growth hormone-mediated pathways and ghrelin-mediated signaling pathways. Curr Opin Pharmacol. 2010; 10: 408-424.

38. Dorshkind K, Horseman ND. The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency. Endocr Rev. 2000; 21: 292-312

39. Lamberts S, van den Beld A, van der Lely A. The endocrinology of aging. Science. 1997; 278: 419-424.

40. Lelic A, Verschoor CP, Ventresca M, Parsons R, Evelegh C, et al. The polyfunctionality of human memory CD8+ T cells elicited by acute and chronic virus infections is not influenced by age. PLoS Pathog. 2012; 8:e1003076.

41. Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010; 5: 99-118.

42. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, et al., "Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans," Mechanisms of Ageing and Development. 2007; 128: 92-105.

43. Cavanagh M, Weyand C, Goronzy J. Chronic inflammation and aging: DNA damage tips the balance. Curr Opin Immunol. 2012; 24: 488-493.

44. Agrawal A, Gupta S. Impact of aging on dendritic cell functions in humans. Ageing Res Rev. 2011; 10: 336-345.

45. Huang MC, Liao JJ, Bonasera S, Longo DL, Goetzl EJ. Nuclear factor-kappaB-dependent reversal of aging-induced alterations in T cell cytokines. FASEB J. 2008; 22: 2142-2150.

46. Salminen A, Huuskonen J, Ojala J, Kauppinen A, Kaarniranta K, et al. "Activation of innate immunity system during aging: NF-5B signaling is the molecular culprit of inflamm-aging," Ageing Res Rev. 2008; 7: 83-105.

47. Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, et al. An update on inflamm-aging: mechanisms, prevention, and treatment. Journal of immunology research, 2016.

48. Monica F, Jaima M. "An update of the oxidationinflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging," Current Pharmaceutical Design. 2009; 15: 3003-3026.

49. Giunta S. "Is inflammaging an auto[innate]immunity subclinical syndrome?" Immunity and Ageing. 2006; 3: 12.

50. Alberti S, Cevenini E, Ostan R, Capri M, Salvioili S, et al. "Age-dependent modifications of Type 1 and Type 2 cytokines within virgin and memory CD4+ T cells in humans," Ageing Res Rev. 2006; 127: 560-566.

51. Franceschi C, Valensin S, Bonafe M, Paolisso G, Yashin AL, et al., "The network and ` the remodeling theories of aging: Historical background and new perspectives," Exp Gerontol. 2000; 35: 879-896.

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52. Martinis MD, Franceschi C, Monti D, Ginaldi L. “Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity,” FEBS Letters. 2005; 579: 2035-2039.

53. Pes GM, Lio D, Carru C, Deiana L, Baggio G, et al., “Association between longevity and cytokine gene polymorphisms. A study in Sardinian centenarians,” Aging Clin Exp Res. 2004; 16: 244-248.

54. Hewitt G, Jurk D, Marques DM, Correia-Melo C, Hardy T, et al., “Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence,” Nature Communications. 2012; 3: 708

55. Olivieri F, Albertini MC, Orciani M, Ceka A, Cricca M, et al., “DNA damage response (DDR) and senescence: shuttled inflamma-miRNAs on the stage of inflamm-aging,” Oncotarget. 2015; 6: 35509-35521.

56. Bonafe M, Storci G, Franceschi C. “Inflamm-aging of ` the stem cell niche: breast cancer as a paradigmatic example: breakdown of the multi-shell cytokine network fuels cancer in aged people,” BioEssays. 2012; 34: 40-49.

57. Mizushima N, Yoshimori T, Levine B. “Methods in mammalian autophagy research,” Cell. 2010; 140: 313- 326.

58. Hur KY, Jung HS, Lee MS. “Role of autophagy in 5- cell function and mass,” Diabetes Obes Metab. 2010; 12: 20-26.

59. White E, Lowe SW. “Eating to exit: autophagy-enabled senescence revealed,” Genes Dev. 2009; 23: 784-787.

60. Juhasz G, Erdi B, Sass M, Neufeld TP. “Atg7-dependent ´ autophagy promotes neuronal health, stress tolerance, and longevity but is dispensable for metamorphosis in Drosophila,” Genes Dev. 2007; 21: 3061-3066.

61. Franceschi C, Valensin S, Lescai F, Olivieri F, Licastro F, et al., “Neuroinflammation and the genetics of Alzheimer’s disease: the search for a proinflammatory phenotype,” AGING CLIN EXP RES.. 2001; 13:163-170.

62. Lencel P, Magne D. “Inflammaging: the driving force in osteoporosis?” Med Hypotheses 2011; 76: 317-321.

63. Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, et al. “Inflammaging as a prodrome to Alzheimer’s disease,” J Neuroinflammation. 2008; 5: 51.

64. Boren E, Gershwin ME.“Inflamm-aging: autoimmunity, and the immune-risk phenotype,” AUTOIMMUN REV. 2004; 3: 401-406.

65. Sipos F, Leiszter K, Tulassay Z. “Effect of ageing on colonic mucosal regeneration,” World J Gastroenterol. 2011; 17: 2981-2986.

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